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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,747	10/16/2003	Helen M. Blau	SUPP-P01-011	1982

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,747	BLAU ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 35-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed 9/5/2006 is acknowledged. No claim has been amended. Claims 1-40 are pending, however, claims 1-33, 35-38 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 34, 39, and 40 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 39, 40 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and following.

In the Remarks, the applicant first argue that *Sigurjonsson et al* cited by the Office teach the microenvironment in the regenerating spinal cord of the chicken embryo stimulates substantial proportions of adult human HSCs to differentiate into full-fledged neurons.

In response, the segment of *Sigurjonsson et al* cited by the applicant refers to ***in vitro*** conditions designed to promote neuronal differentiation such as the **regenerating** spinal cord of the chicken **embryo**, which is significantly different from the claimed invention directed to

mobilization of bone marrow cells *in vivo* in a fully developed human being, and achieving therapeutic effect on neuronal deficiency. Indeed, *Sigurjonsson et al* (PNAS 205;102:5227-32) acknowledges higher incidences have been reported for HSCs and other bone marrow stem cells *in vitro* under conditions designed to promote neuronal differentiation, after pointing out insufficient rate of neuronal differentiation *in vivo*, which fails to provide any therapeutic effect for any disease, "ADULT HSCS FROM RODENTS AND HUMANS INJECTED INTRAVENOUSLY OR INTRACEREBRALLY INTO RODENT HOSTS CAN SETTLE IN THE BRAIN AND EXPRESS NEURONAL MARKERS, BUT THE INCIDENCE OF NEURONAL DIFFERENTIATION HAS NEVER BEEN REPORTED TO EXCEED 1-2% OF THOSE HSCS THAT INTEGRATE INTO THE BRAIN" (column 2, page 5227, emphasis added). Clearly, at such a low rate of neuronal differentiation, and uncertainty of neuron phenotype and function *in vivo*, any therapeutic effect of mobilized BMDCs on treating a neuronal deficiency would be remote at the time of instant filing date. In a post-filing publication, instant inventor concurs (*Pomerantz & Blau*, Nat Cell Biol 2004;6:810-6), "MAJOR CHALLENGES EXIST IN THE USE OF BMDCS IN A CELL-BASED THERAPY FOR NON-HEMATOPOIETIC TISSUES, INCLUDING INCREASING THEIR EFFICIENCY OF INCORPORTION INTO TARGET TISSUES AND DEMONSTRATING EFFICACY IN TREATING TISSUE MALFUNCTION" (column 2, page 810). The authors are optimistic for the emerging potential of BMDCs, but the reality was, and still is, that the state of the pertinent art has not developed to the extent that enabling a therapeutic use for ameliorating any symptom of a neuronal disorder at the time of instant priority date.

The applicant then argue the exact dose and the number of treatment for each patient may vary, and the details of a therapeutic method is not required for the method to be patentable.

In response, the statue under 35 U.S.C 112, first paragraph requires "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, AND OF THE MANNER AND PROCESS OF

MAKING AND USING IT, **IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS** AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION" (emphasis added). "**IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING**". In the instant case, using bone marrow cell mobilization therapy to treat neuronal deficiency is a novel idea presented by instant applicant, little is known in the art about how to make this idea feasible, and the state of the art is such that years after instant priority date, there is no known means that is sufficient for treating neuronal deficiency, and hence it is upon the applicant to provide an enabling disclosure to guide the practice of instantly claimed invention at the time of instant filing date. The MPEP states, "**THERE MAY BE TIMES WHEN THE WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE A REASONABLE DOUBT AS TO THE ACCURACY OF A PARTICULAR BROAD STATEMENT PUT FORWARD AS ENABLING SUPPORT FOR A CLAIM.** THIS WILL ESPECIALLY BE THE CASE WHERE THE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES. MOST OFTEN, ADDITIONAL FACTORS, SUCH AS THE TEACHINGS IN PERTINENT REFERENCES, WILL BE AVAILABLE TO SUBSTANTIATE ANY DOUBTS THAT THE ASSERTED SCOPE OF OBJECTIVE ENABLEMENT IS IN FACT COMMENSURATE WITH THE SCOPE OF PROTECTION SOUGHT AND TO SUPPORT ANY DEMANDS BASED THEREON FOR PROOF. [FOOTNOTE OMITTED.] (MPEP 2164.02, 03). Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific

> starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to describe any specific agent or condition under which and using such agent the bone marrow cell mobilization therapy can be carried out, and it fails to teach what kind of effect in the brain tissue one is to expect upon the stem cell mobilization, and hence there is a failure to meet the enablement requirement.

Applicant then cited several publications in the art to support the argument that G-CSF treatment has been demonstrated to produce a significant mobilization of stem cells in humans.

In response, it is noted two of the three cited references are post-filing date publications, the sole pre-filing date reference only acknowledges the mobilized stem cells help the recovery of blood cells, and **none** of these publications address the effect of mobilized bone marrow cells on **neuronal system**. Hence, they fail to provide an enabling disclosure to support instantly claimed invention.

The applicant goes on to argue that instant specification demonstrates that bone marrow-derived cells contribute to neuronal cells.

In response, although it had become known at around time of instant filing that bone marrow cells have the potential to differentiate into neuronal cells (*Kopen et al*, PNAS 1999;96:10711-6; *Sanchez-Ramos et al*, Exp Neurol 2000;164;247-56; *Mezey et al*, Science 2000;290:1779-82), which has the potential for neuron regeneration, the state of the art was in the infant stage of development, and the bone marrow mobilization treatment or bone marrow

transplantation was far from treating any neuronal diseases. The inefficiency of such differentiation, and the unknown function of the differentiated cells that bear neuron surface markers, among others, are a few of the reasons that art needs further development to reach the level of therapeutic use.

In light of the state of the art as discussed *supra*, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Although the instant specification provides preliminary studies on migration, relocation, and contribution of transplanted BMDCs to Purkinje neurons in the brain, it fails to teach whether a BM cell mobilization therapy would boost relocation of bone marrow cells to the brain, and cause their differentiation into neurons in a sufficient quantity and quality. The specification fails to teach the efficacy of such BM mobilization processes, whether it is sufficient to the extent that any clinical benefit could be observed for treating a neuronal deficiency.

Moreover, the observation of neuronal differentiation occurred in the circumstance where the recipient received lethal irradiation and BM cell transplantation, where instant claims are drawn to administering cytokines G-CSF/GM-CSF without any cell transplantation. It is unknown, unpredictable, and the specification fails to teach whether the neuronal differentiation would occur just giving a growth factor G-CSF. Accordingly, the specification fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34, 39, 40 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because they fail to clearly set forth the method step(s). The method provides for administering "a bone marrow mobilization therapy", however, there is no step clearly set forth the therapeutic regimen. It is unclear what step the "mobilization therapy" includes, and thus the metes and bounds of the claims are unclear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

In the remarks, the applicant argues that a bone marrow mobilization therapy is well known in the art citing specification and several references to support the argument.

In response, Applicants are reminded that Claims must, under modern claim practice, stand alone to define invention, since, in patentability context, claims are to be given their broadest reasonable interpretations, and since limitations are not to be read into claims from specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. *In re Paulsen* 30 F.3d 1475, 1480, 31 USPQ 2d 1671, 1674 (Fed. Cur,1994); *Intervet America Inc. v. Kee-Vet Lab. Inc.*, 887 F.2d 1050, 1053, 12 USPQ 2d 1474, 1476 (Fed. Cir. 1989). Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with

a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. Janice Li, M.D.
Primary Examiner
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PRIMARY EXAMINER

QJL
November 27, 2006